A Scoping Review of the Incidence, Predictors, and Outcomes of Delirium Among Critically Ill Stroke Patients

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ABSTRACT

BACKGROUND: Delirium is a common, often iatrogenically induced syndrome that may impede the physical, cognitive, and psychological recovery of critically ill adults. The effect delirium has on outcomes of intensive care unit patients having acute neurologic injury remains unclear because previous studies frequently exclude this vulnerable population. The aim of this scoping review was to describe the incidence, predictors, and outcomes of delirium among adults admitted to an intensive care unit experiencing an acute ischemic stroke, intracerebral hemorrhage, or aneurysmal subarachnoid hemorrhage. **METHODS:** PubMed, CINAHL, Web of Science, EMBASE, and Scopus were searched with the terms (1) *stroke*, (2) *critical care*, and (3) *delirium*. Inclusion criteria were original peer-reviewed research reporting the incidence, outcomes, or predictors of delirium after acute stroke among critically ill adults. Editorials, reviews, posters, conference proceedings, abstracts, and studies in which stroke was not the primary reason for admission were excluded. Title and abstract screening, full-text review, and data extraction were performed by 2 authors, with disagreements adjudicated by a third author. **RESULTS:** The initial search yielded 1051 results. Eighteen studies met eligibility criteria and were included in the review. Stroke type was not mutually exclusive and included persons given a diagnosis of acute ischemic stroke (11), intracerebral hemorrhage (12), aneurysmal subarachnoid hemorrhage (8), and other (1) strokes. Incidence of delirium among stroke patients ranged from 12% to 75%. Predictors of delirium included older age, preexisting dementia, higher severity of illness, and physical restraint use. Outcomes associated with delirium included higher mortality, longer length of stay, worse cognition and quality of life, and lower functional status. **CONCLUSIONS:** Current findings are limited by heterogenous populations, assessments, and measurement parameters. Detection and management of delirium among critically ill stroke patients requires an approach with specific considerations to the complexities of acute neurological injury and concomitant critical illness.

Keywords: cerebral hemorrhage, cerebral infarction, critical illness, delirium, incidence, outcomes, precipitating factors, stroke, subarachnoid hemorrhage

Delirium is an acute disturbance in attention, awareness, and cognition that occurs as a direct physiologic response to illness, another medical condition, substance intoxication or withdrawal, exposure to a toxin, or due to multiple etiologies.[1] Delirium arises when a number of predisposing (eg, age, preexisting cognitive impairment)[2] and precipitating (eg, sedatives, mechanical ventilation)[2] risk factors interact.[3] Patients with multiple predisposing factors may experience an episode of delirium from a single, mild precipitating insult, whereas a previously healthy individual may become delirious if exposed to multiple precipitating risk factors.[3] This complexity may explain why intensive care unit (ICU) patients, who are often

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severely ill and exposed to multiple deliriogenic medications, are at a particularly high risk for developing delirium.

Current estimates suggest ICU delirium rates range from 18.9% to 83% among diverse cohorts of critically ill patients.[2,4,5] Decades of research suggest ICU-acquired delirium is associated with poor clinical outcomes. In a variety of ICUs, delirium has shown to be an independent predictor of prolonged hospital and ICU length of stay (LOS);[6] higher ICU,[7] hospital,[7,8] and 6-month mortality;[8] prolonged mechanical ventilation;[7] postdischarge disability;[9] and severe long-term cognitive impairment.[10]

Delirium may have an important role in stroke recovery; however, acute and chronic neurologic disease among critically ill patients creates significant challenges to detection and treatment of delirium. Because sequelae of an acute neurological injury can obscure accuracy of delirium assessments, much of the delirium research to date excluded subjects with neurological injury.[10,11] Common detection tools for delirium in critical care may not be accurate for patients with stroke due to concomitant brain injury, pronounced neurological deficits such as hemineglect and aphasia, and low level of arousal.[11–13] Thus, extrapolation of previous findings to critically ill patients experiencing an acute stroke may not be appropriate or feasible, and data are needed to provide direction for clinical management of delirium in this high-risk population.

The purpose of this scoping review is to identify important knowledge gaps in the assessment, prevention, and management of delirium in critically ill adults admitted to an ICU after having acute stroke by identifying the nature, extent, quality, and quantity of the available literature on this increasingly important topic. Specifically, we describe the incidence, predictors, and outcomes of delirium among critically ill patients with stroke subtypes including acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and aneurysmal subarachnoid hemorrhage (aSAH).

Methods

This review adhered to accepted methods for scoping reviews,[14] with findings reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews.[15] A structured review protocol was created a priori to establish the specific aims of the search, inclusion and exclusion criteria, and fields for data extraction. Covidence systematic review software (Veritas Health Innovation) was used for all stages of the review process. The librarian-assisted search strategy is detailed in the Supplemental Digital Content (see Table, Supplemental Digital Content 1, available at http://links.lww.com/JNN/A399). The terms stroke (AIS, ICH, and aSAH), critical care, and delirium were each expanded with inclusive synonyms. Searches were performed in January 2020 in PubMed, CINAHL, Web of Science, EMBASE, and Scopus.

Studies report the incidence of delirium ranges from 11.8% to 75%.

Included in this scoping review were original peer-reviewed research studies, published in English, that reported the incidence, predictors, or outcomes of delirium among adult acute stroke patients, who were admitted to an ICU. Inclusion required reporting measurement of delirium with a valid and reliable tool or using established criteria. Excluded were editorials, reviews, posters, conference proceeding, abstracts, and studies in which stroke was not the primary reason for ICU admission.

Studies were imported into the Covidence software, and duplicates were removed. Title and abstract screening and then full-text review were first performed by 2 authors, with disagreements adjudicated by a third author. A PRISMA flowchart covering the screening process was created (Supplemental Digital Content 2: PRISMA flowchart, available at http://links.lww.com/JNN/A400).

Data were extracted from included articles using a structured extraction tool. Variables extracted included patient characteristics (age, diagnosis, stroke type, stroke severity, systemic severity of illness, and mechanical ventilation status), setting (type of ICU, critically ill subgroup from a mixed acuity study), delirium measurement strategy, incidence, prevalence, predictors of delirium, and outcomes.

Results

The search yielded 1051 articles. After removing duplicates, 758 studies were screened by abstract. One hundred seven studies underwent full-text review, and 18 including 2386 stroke patients were eligible for inclusion. Thirteen studies used a prospective cohort design.[16–28] Not all samples were exclusively stroke patients or exclusively ICU patients. There was wide variation in the setting among included studies. Six included only patients in a dedicated neurocritical care unit.[20,21,23,25,27,29] Four used mixed-specialty ICUs (eg, medical-surgical ICU), which reported on a subgroup of stroke patients.[16,17,19,22,28] Five reported mixed acuity stroke units, where critically ill stroke patients were reported as a subgroup within an acute stroke population.[18,22,24,30,31] Four did not explicitly include setting information but included acuity consistent with ICU care (Table, Supplemental Digital Content 3: summary of included studies, available at http://links.lww.com/JNN/A401).

When reviewing stroke diagnosis across studies, 11 reported on AIS,[16,18,20–22,24,28,30–33] 12 reported on ICH,[16,18,20–26,28,30,32] 8 reported on aSAH,[16,17,20,21,28,30–32] and 1 did not report stroke type.[27] Only 3 studies reported anatomic stroke subtypes.[18,30,31] Only 4 reported stroke severity.[18,22,32,33] These 4 used the National Institutes of Health Stroke Scale (NIHSS), with scores ranging from 9 to 19 and mean NIHSS scores reported as 9,[22] 11,[18] 14,[32] and 19.[33]

Systemic severity of illness was reported in 6 studies; 4 used the Acute Physiologic Assessment and Chronic Health Evaluation II score,[19,21,27,28] and 3 used the sequential organ failure assessment score.[18,19,22] Higher severity of illness among patients who developed delirium was reported by several studies.[18,19,27] Mechanical ventilation status was reported in 7 studies[16,19,22,25,28,30,33] with 7% to 81% of patients requiring mechanical ventilation.

Eleven studies[18–25,27,30,31] reported data on the incidence or prevalence of delirium (Table 1). Delirium incidence ranged from 11.8% to 75.0%, with most exceeding 30%. Two studies reported delirium prevalence ranging from 42.2% to 44.4%.[19,27] Studies that did not provide a subgroup analysis for stroke patients were excluded from Table 1. Of the studies reporting incidence or prevalence, 9 measured delirium with a Confusion Assessment Method (CAM) derivative,[18,19,21–25,27,31] and 2 used the Intensive Care Delirium Screening Checklist (ICDSC).[20,30] Three studies used *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria as the comparator for ICU delirium assessment.[18,22,24] Two studies used parallel CAM derivatives with *DSM*–based criteria.[18,24] One also used the CAM-ICU with paired *DSM-IV* based evaluations within 2 hours by experienced experts.[22] They reported the following CAM-ICU psychometrics (95% confidence interval [CI]): sensitivity, 76% (54.9%-90.6%); specificity, 98.1% (93.2%-99.8%); positive predictive value, 90.5% (69.6%-98.8%); negative predictive value, 94.4% (88.3%-97.9%); and overall accuracy, 93.8% (88.2%-97.3%).

Eight studies evaluated predictive factors for delirium (Table 2).[16,18–20,24,26,27,30] Common predictors reported in 3 or more studies included older age,[16,18–20,24] history of stroke,[19,24,30] preexisting dementia,[18–20,24,30] higher severity of illness,[18,19,27] and use of physical restraints.[19,20,27] Several stroke-related characteristics were noted to be predictors of delirium: higher ICH volume,[18] left-sided stroke,[24] higher NIHSS score,[24] and total anterior circulation infarct.[18] Two studies reported no statistically significant relation between anatomy and risk of developing delirium.[30,31]

Six studies included information on outcomes after an episode of ICU delirium during acute stroke (Supplemental Digital Content 4: outcomes following delirium in acute stroke, available at http://links.lww.com/JNN/A402).[22,23,25,27,28,31] A prospective cohort study found delirious stroke patients had an insignificant trend toward higher in-hospital and 6-month mortality rates.[22] A case-control study on long-term cognitive outcomes after AIS and ICH noted a higher 2-year mortality among the delirious group when compared with nondelirious cohorts (49.2% vs 26.2%, respectively).[31]

Two studies reported outcomes using the modified Rankin scale (mRS).[23,27] A study of ICH patients found 1 point higher (worse) median mRS at 14 days after discharge among delirious patients.[23] Multivariate models also indicated higher odds of poor outcome (mRS $\geq$ 3) at 28 days from symptom onset among delirious patients, when controlling for admission NIHSS and age. These findings did not persist at 3 and 12 months. Another study reported higher 28-day mRS among delirious ICH patients when compared with similar cohorts who did not experience delirium.[25]

Four studies reported increased hospital or ICU LOS across all types of stroke patients who experienced delirium. Three studies reported a significantly higher number of days,[22,23,27] and a fourth study noted a 10% increase in ICU LOS for each 1-point increase in ICDSC score (P = .0131).[28]

One study reported on the relationship between delirium and dementia after stroke. Two years after stroke (all subtypes), patients who experienced delirium during the acute phase had significantly higher rates of dementia on 2 separate dementia scales (77.3% vs 32.1% [P < .01] with the Rotterdam-Cambridge Cognition Examination; 50% vs 14.3% [P < .01] with the Clinical Dementia Rating scale).[31] In this study, delirium during hospitalization was reported to be a risk factor for developing dementia when controlling for age (odds ratio, 7.2; 95% CI, 1.88-27.89).[31]

Four studies evaluated cognitive function among mixed populations of stroke subtypes and compared outcomes between those who experienced delirium during initial hospitalization to those who did not. One study reported poorer scores at 2-year follow-up in the following domains: verbal memory (P = .02), attention (P = .04), visual construction (P = .02), language (P = .04), and executive function (P = .03).[31] In a population of patients with ICH, those who had delirium and agitation had significantly worse cognitive function on health-related quality of life scores at 28 days and 1 year than those who had delirium without agitation or those who had no delirium (P = .006).[25] Mini-Mental State Examination scores at hospital discharge among those with delirium were 6 points lower compared with no Mini-Mental State Examination decrease among those without delirium (P < .05).[27]

TABLE 1. Incidence and Prevalence of Delirium in Critically Ill Stroke Patients

Author (Year)	Incidence and Prevalence	Delirium Scale	Stroke Type	Motor Subtypes	Onset	Duration
Hosoya (2018)	97 (36%) and NR	ICDSC	AIS, ICH, and aSAH	NR	2.5 (2.1) d	NR
Kostalova (2012)	43 (43%) and NR	*DSM-IV* and CAM-ICU	AIS and ICH	NR	65.9% within the first day	NR
Limpawattana (2016)	22 (22.2%) and 44 (44.4%)	CAM-ICU	AIS	Hyper, 16 (36.4%); mixed 15 (34.1%); hypo, 13 (29.5%)	9 of 22 (20.45%) on day 1, all within 5 d	NR
Matano (2017)	29 (13.2%) and NR	ICDSC	Mixed	NR	NR	NR
McLaughlin (2018)	15 (75%) and NR	CAM-ICU	Mixed	Hyperactive more common	NR	NR
Mitasova (2012)	55 (42.6%) and NR	CAM-ICU (cz) and *DSM-IV*	AIS and ICH	295 patients; days of delirium: 111 hypo, 78 hyper, and 109 mixed	67.3% on the first day of admission	NR
Naidech (2013)	31 (27%) and NR	CAM-ICU	ICH	"Nearly always hypoactive"	5.9 (6.1) d	1-3 d
Pasinska (2018)	203 (27.1%) and NR	bCAM, CAM-ICU, *DSM-V*	AIS and ICH	DMS-4: hyper, 31 (15.27%); hypo, 85 (41.87%); mixed, 77 (39.93%); unspecified, 10 (4.93%)	NR	NR
Rosenthal (2017)	53 (30%) and NR	CAM-ICU	ICH	NR	NR	NR
van Rijsbergen (2011)	62 (11.8%) and NR	CAM	AIS and ICH	NR	NR	NR
Wang (2018)	54 (42.2%) and 42.2%	CAM-ICU (Chinese)	Mixed	17 (31.5%) hyper, 21 (38.9%) hypo, 16 (29.6%) mixed	57.4% within 2-5 d; median time to onset, 4.5 d	NR

Values are frequency (percentage) or mean (SD).
Abbreviations: AIS, acute ischemic stroke; aSAH, aneurysmal subarachnoid hemorrhage; bCAM, brief CAM; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; cz, Czech-language variant; DMS-4, Delirium Motor Subtype Scale-4; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; *DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; ICDSC, Intensive Care Delirium Screening Checklist; ICH, intracerebral hemorrhage; NR, not reported.

TABLE 2. Significant Predictors of Delirium After Stroke

Author (Year)	Common Predictors	Other Predictors
Dittrich (2016)	Age	Number of catheters and drains, male sex
Hosoya (2018)	Preexisting dementia Prior stroke	Ventricular drainage, somnolence, aphasia, ureter tube, home anxiety or sleep medications
Kostalova (2012)	Age Preexisting dementia Severity of illness	ICH, higher serum creatinine, bilirubin, GGT, lower PLT, lesion volume > 40 mL, total anterior circulation infarct
Limpawattana (2016)	Age Preexisting dementia Pneumonia Severity of illness Physical restraints Previous stroke	Baseline functional status, depression, polypharmacy, sleep deprivation, multiple bed changes, Foley catheter, mechanical ventilation
Matano (2017)	Age Preexisting dementia Physical restraints	Severe white matter lesions, surrounding patients who were monitored or getting suctioned, surrounding patients with delirium
Pasinska (2018) [hyperactive delirium]	Age Preexisting dementia Pneumonia	NIHSS, spatial neglect, visual disorders, DM, atrial fibrillation, coronary artery disease, anxiety, comorbidity index, heparin, leukocytosis, UTI, motoric disorders
Pasinska (2018) [hypoactive delirium]	Age Preexisting dementia Pneumonia Previous stroke	NIHSS, aphasia, left-sided stroke, vision disorders, spatial neglect, ICH, premodified Rankin scale, sleep disorder, depression, higher comorbidity score, anticoagulants, insulin, β-blockers, leukocytosis, hyperglycemia, fever, UTI, male sex, lower education, smoker
Sániová (2012)		Higher GCS score
Wang (2018)	Severity of illness Physical restraint	Sleep deprivation, fever

Abbreviations: DM, diabetes mellitus; GCS, Glasgow Coma Scale; GGT, gamma-glutamyl transferase; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; PLT, platelets; UTI, urinary tract infection; WBC, white blood cell.

Patients who were ever delirious had worse quality of life in the domains of applied cognition, executive function, and fatigue at all follow-up time points (28 days, 3 months, 1 year), even after correction for age, NIHSS on admission, and any benzodiazepine use (28-day neuro-Quality of Life in Neurological Disorders *T* score of 5.8 [0.58 SD lower than the never-delirious group]; 95% CI, 0.15-11.5; $P = .045$).[23]

Discussion

In this scoping review, we identified 18 studies reporting incidence, predictors, or outcomes among critically ill stroke patients. Overall incidence of delirium during hospitalization among stroke patients in critical care settings ranged from 11.8% to 75%, with 66% of studies reporting rates from 22% to 43%.[21] These findings are consistent with rates among general ICU populations. A systematic review and meta-analysis among all types of ICU patients found an overall pooled prevalence of delirium of 31%.[34] Our included studies of critically ill stroke patients provided rates of delirium comparable with this, but with a broad range. Rates of delirium incidence in other ICU populations also vary considerably, with medical ICUs ranging from 9% to 24%, surgical ICUs ranging from 3% to 54%, and mixed ICUs ranging from 24% to 45% in a meta-analysis.[2] This variability in incidence, as with our variability, suggests individualized predictive factors may contribute to the differential development of delirium.

Studies included in our review reported predictors of delirium include age, preexisting dementia, and severity of illness, which are consistent with predictive models in the general ICU literature.[35] Other predictors reported in the general ICU literature, but not noted in studies included in this review, included metabolic acidosis, infection, sedatives, urea concentration, coma, emergency surgery, emergency admission, corticosteroids, and mechanical ventilation.[35] The predictive models from the general ICU literature did not consistently include neurological patients. This literature on critically ill stroke patients shares some predictors in common with the general ICU literature but omits several key predictors of delirium, particularly mechanical ventilation.

The findings in our review indicate that delirium is associated with higher mortality, longer hospital and ICU LOS, and long-term cognitive deficits after stroke, which is consistent with general critical care literature. A meta-analysis of delirium among 16 595 general critically ill patients found an increased risk ratio for death during admission among delirious patients of 2.19 (95% CI, 1.78-2.70; $P < .001$).[7] In our review, only 2 studies reported increased mortality; however, they did not provide multivariate models to determine the role of confounding variables when predicting mortality.

Delirium has historically been considered a transient condition that abates after the precipitating factor resolves. However, our findings of worse cognitive and functional outcomes among both ICH and mixed-stroke populations at 14 days,[23] 28 days,[23,25] 3 months and 1 year,[25] and 2 years[31] suggest otherwise. These findings are consistent with medical ICU survivors where delirium is associated with worse cognitive outcomes at 3 and 12 months.[36] Another study found longer duration of delirium led to worse functional status.[37] As stroke is associated with cognitive decline from both vascular dementia and neurodegenerative processes and delirium is also associated with cognitive decline after a variety of acute illnesses, disentangling delirium's contribution after a stroke will help guide targeted interventions for post-ICU care.

Most studies used the CAM-ICU or ICDSC to measure delirium, consistent with other critical care literature.[34] Data on which scale is most appropriate, particularly among patients with acute neurological insults, remain inconclusive. Larsen et al[38] reported 85% sensitivity and 75% specificity for the ICDSC in a neurocritical care population but poor rates for the CAM-ICU (59% and 56%, respectively). Conversely, Mitasova et al[22] found 76% sensitivity and 98% specificity for the CAM-ICU in AIS and ICH patients compared with *DSM-IV* criteria. Others suggest neither the CAM-ICU nor the ICDSC is accurate for use in a neurocritical care or stroke unit population.[12] However, definitive consensus on the appropriateness and use of these scales among critically ill stroke patients remains elusive.[39,40]

Limitations

Use of scoping review as a methodology and the narrow scope of the literature available on this topic can limit the ability to provide implications for practice. The absence of common data elements between studies precluded our ability to consider quantitative meta-analysis. Although we prespecified a comprehensive search strategy involving 5 medical databases, it is possible that pertinent studies were missed, particularly those that may have included stroke patients with delirium outside a traditional or specific type of ICU setting. We incorporated an inclusive search strategy to capture any reports of delirium among stroke patients that required an ICU admission. As a result, some of the studies included in this review reported on stroke patients in mixed acuity settings. To address this limitation but still adhere to our inclusive approach, we only included reports if a subgroup analysis on critically ill stroke patients was included or acuity measures indicated need for an ICU admission. However, it is possible that estimates reported in our review may be slightly different if a less inclusive approach was used.

Conclusion

Delirium continues to be a pervasive problem among critically ill stroke patients. Current research findings are limited by heterogenous populations, assessments, and measurement parameters. Detection and management of delirium among critically ill stroke patients requires a targeted approach with specific considerations to the complexities of acute neurological injury and concomitant critical illness. Investigations specific to critically ill stroke patients are needed to advance the science and subsequent practice recommendations for delirium management in this high-risk population.

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